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Physicochemical and dissolution studies of simvastatin solid dispersions with Pluronic F127

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Simvastatin (SIM) solid dispersions with Pluronic F127 (PLU) obtained by kneading and fusion methods were characterized by differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and Fourier Transform Infrared Spectroscopy (FTIR). DSC studies demonstrate that the SIM/PLU solid dispersions formed a simple eutectic phase diagram. FTIR spectroscopy and XRPD studies of obtained mixtures showed no interaction between the components in the solid state and confirmed the absence of terminal solid solutions. Intrinsic dissolution studies of solid dispersions in 0.5% sodium lauryl sulfate solution (SLS) indicated that the dissolution rate markedly increased in these solid dispersions systems compared with pure SIM. The increase in dissolution rate strongly depended on ratios of drug to carriers and selection of the method of preparations of mixtures. The solid dispersions prepared in the weight ratios of 60.0/40.0% and 69.9/30.1% w/w of SIM/PLU by the kneading method showed the highest improvement in wettability and dissolution rate of SIM. Approximately 100% of the drug was dissolved from these mixtures in comparison to 3.84% of pure simvastatin within 120 min.

1. Introduction

Simvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA), blocking the conversion of HMG-CoA to mevalonate on the early biosynthesis of cholesterol in the body (Pandya et al. 2008). SIM, except for its pharmacological effect on lipid metabolism, has pleiotropic effects including a cytoprotective effect on the vascular endothelium, inhibition inflammation, atherosclerotic plaque stabilization and a positive influence on the coagulation system and fibrinolysis (Wierzbicki et al. 2003; Veillard and Mach 2002; Zhou et al. 2010). Increasing evidence suggests that statins exhibit therapeutic effects in the treatment of cancer (Miller et al. 2011) and certain skin diseases (Jowkar and Namazi 2010).

Simvastatin is characterized by low solubility and acceptable permeability through biomembranes, which places it in class II of the Biopharmaceutics Classification System (BCS) (Rao et al. 2010; Silva et al. 2010). It is therefore important to increase its solubility and dissolution rate in order to achieve a greater bioavailability of the substance from solid oral dosage forms (Pandya et al., 2008). There are many methods to improve the dissolution profile of poorly water soluble drugs. Such approaches include micronization, solubilization, the use of polymorphs, inclusion complexation, dendrimer complex, the addition of surfactants, salt formation, the use of prodrugs, pH adjustment and solid dispersion technique (Fahr and Li 2007; Gomez-Orellana 2005; Leuner and Dressman 2000; Winter de Vagas 2012). Preparation of solid dispersions (SDs) is one of the most effective and promising techniques used to resolve the poor aqueous solubility and dissolution rate of simvastatin (Murtaza 2012; Tiwari and Pathak 2011). The improved drug dissolution rate from SDs is explained by the reduced particle size, reduced agglomeration, changes in the physical state of the drug, increased surface area and wettability, and higher degree of porosity (Dhirendra et al. 2009; Janssens and Van den Mooter 2009). Many polymers and other pharmaceutical excipients were employed in order to improve the solubility of SIM, such as hydroxypropyl-β-dextrin (Mandal et al. 2010), PEG 4000 and PEG 6000 (Mandal et al. 2010; Silva et al. 2010), PVP K15 (Silva et al. 2010), PVP K30 (Patel and Patel 2008; Rao et al. 2011), Poloxamer 188 (Rao et al. 2011), HPMC K3LV (Pandya et al. 2008), sodium starch glycolate, croscarmellose sodium (Rao et al. 2010) and Aerosil 200 (Ambike et al. 2005). Earlier studies showed a significant improvement in the dissolution of SIM by solid dispersion with sodium starch glycolate and croscarmellose sodium prepared by a coevaporation method. *In vitro* dissolution studies showed almost 100% drug release from prepared solid dispersions. A significant decrease in crystallinity of pure drug was also demonstrated, which provided an enhancement in the dissolution rate (Rao et al. 2010). Mandal et al. (2010) prepared solid dispersions of simvastatin with PEG 4000 and PEG 6000 using fusion method and an inclusion complex with HP-β-cyclodextrin prepared by the kneading method. Dissolution studies showed that the dissolution rate was increased from solid dispersion systems compared with physical mixtures and pure simvastatin. About 100% simvastatin were released from inclusion complexes with HP-β-cyclodextrin.

Pluronics are a group of block copolymers which are used for various pharmaceutical applications. A significant improvement

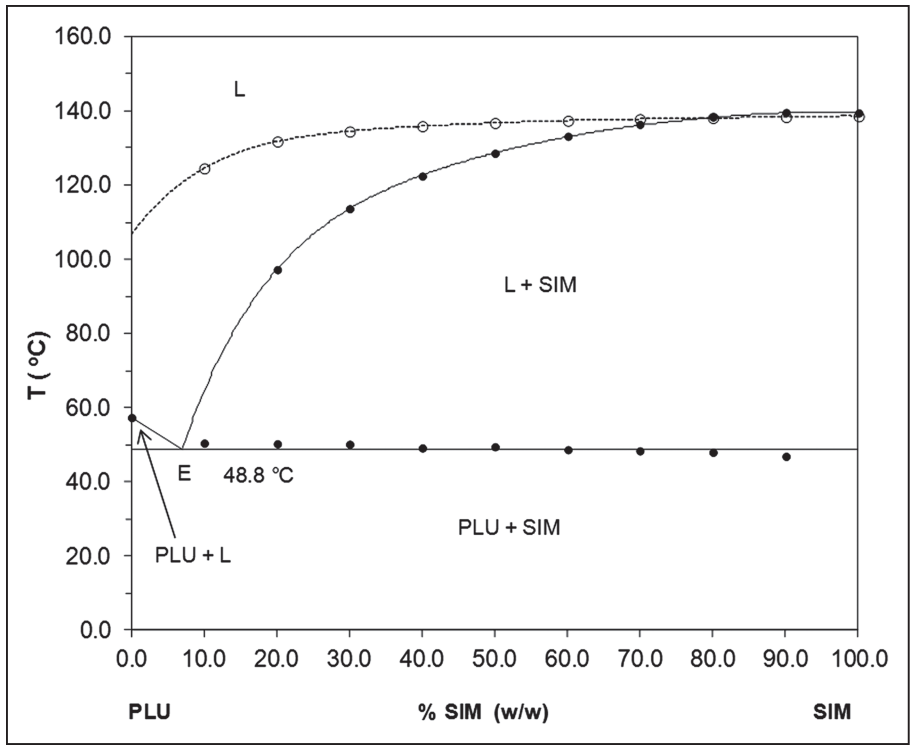

Fig. 1: Phase equilibrium diagram of the simvastatin – Pluronic F127 system: L- liquid, (filled circle) experimental points, (open circle) points calculated from the Schröder-van Laar equation.

of simvastatin saturation solubility was obtained for solid dispersions with Pluronic F68 (Poloxamer 188) prepared by the spray drying method (Rao 2011). However, to our knowledge there is no study of simvastatin solid dispersions with Pluronic F127. Using Pluronic F127 as a carrier in solid dispersions can lead to an enhanced solubilisation of poorly water-soluble drugs (Dumortier et al. 2006), e.g. flufenamic acid (Shazly et al. 2012), glibenclamide (Elbary et al. 2011), ketoconazole (Kumar et al. 2011) and desloratadine (Kolašinac et al. 2012). Pluronic can act as a polymer matrix and as a surface active-agent, leading to a dissolution enhancement of the drug (Shazly et al. 2012).
The present study was planned to improve the aqueous solubility and dissolution rate of simvastatin by developing its solid dispersions with Pluronic F127. Solid dispersion systems were prepared in different weight ratios employing two methods such as kneading and fusion. Solid dispersion systems and pure simvastatin were further characterized by Fourier transform infrared spectroscopy (FTIR), X-ray powder diffractometry (XRPD), differential scanning calorimetry (DSC) and by dissolution studies.

2. Investigations, results and discussion

2.1. Drug content

The simvastatin content of the formulations was found to be in the range of 97.22% to 101.27% of the declared amount. Table 1 lists results from studies of drug content in solid dispersions.

2.2. Differential scanning calorimetry

The formulation of solid dispersions in order to increase the solubility of poorly water soluble active ingredients requires the knowledge of the phase equilibria between the examined components. The simvastatin-Pluronic F127 solid-liquid equilibrium has not been previously specified in detail. Our DSC studies of SIM/PLU solid dispersions indicate the formation of a simple eutectic phase diagram (without the terminal solid solutions). The melting points of the pure components (simvastatin: 139.5 °C, Pluronic F127: 57.4 °C) were depressed due to the existence of the other component in the dispersion as shown in the phase diagram in Fig. 1. As shown in Fig. 2, only two thermal effects can be observed on DSC curves obtained for the studied solid dispersions. The onset of the first peak (temperature of solidus) appears approximately at the same temperature and represents the eutectic reaction: solid simvastatin (SIM) + solid Pluronic F127 (PLU) = liquid (L) at 48.8 °C. The peak position did not vary with the level of component, whereas the magnitude of heat increased with the decrease of simvastatin weight fraction. The second peak, corresponding to the liquidus, was

Table 1: Drug content in prepared solid dispersions

Formulation code	Average content of SIM
10.0/90.0 SIM/PLU-KN	99.86 ± 0.125
20.0/80.0 SIM/PLU-KN	100.16 ± 0.301
30.0/70.0 SIM/PLU-KN	100.46 ± 0.259
40.0/60.0 SIM/PLU-KN	98.64 ± 0.444
50.0/50.0 SIM/PLU-KN	100.04 ± 0.201
60.0/40.0 SIM/PLU-KN	99.66 ± 0.309
69.9/30.1 SIM/PLU-KN	98.21 ± 0.215
80.0/20.0 SIM/PLU-KN	97.23 ± 0.140
90.0/10.0 SIM/PLU-KN	98.72 ± 0.182
10.0/90.0 SIM/PLU-FUS	100.78 ± 0.189
20.0/80.0 SIM/PLU-FUS	101.27 ± 0.331
30.0/70.0 SIM/PLU-FUS	99.45 ± 0.297
40.0/60.0 SIM/PLU-FUS	97.57 ± 0.161
50.0/50.0 SIM/PLU-FUS	98.46 ± 0.206
60.0/40.0 SIM/PLU-FUS	98.21 ± 0.202
70.0/30.0 SIM/PLU-FUS	100.13 ± 0.371
80.0/20.0 SIM/PLU-FUS	99.73 ± 0.227
90.0/10.0 SIM/PLU-FUS	98.50 ± 0.342

Data are expressed as mean ± SD (n = 3).

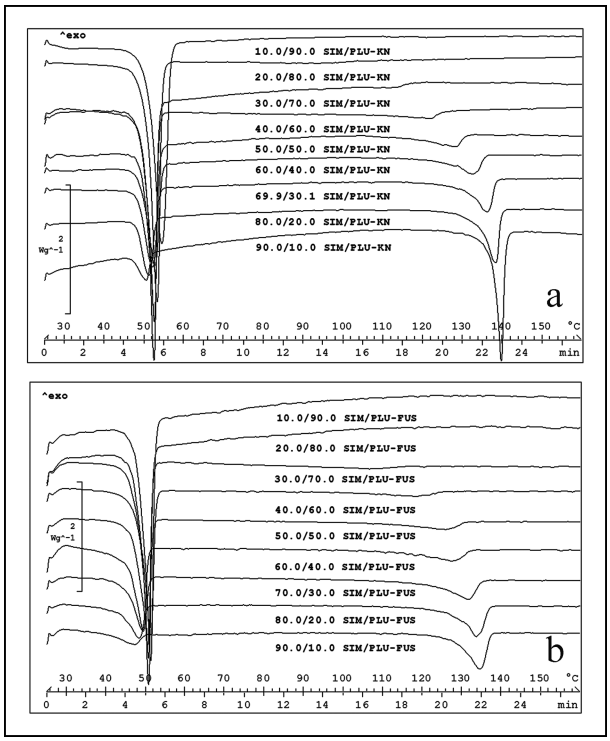

Fig. 2: DSC thermograms of SIM/PLU solid dispersions prepared by: a – kneading method, b – fusion method.

generally wider, indicating that complete melting took place over a temperature range.

Application of the Schroeder-van Laar equation, under an assumption of an ideal system in the liquid phase (Sedláková and Malijevská 2007), allows the calculation of liquid temperature. The comparison of our experimental DSC data (filled circles) with theoretical calculations (open circles), has shown deviations from ideality (Fig. 1), suggesting an intermolecular interactions between drug and polymer. However, a spectroscopic study did not confirm the occurrence of such interactions. Finally the solidus line was established as a straight line drawn at eutectic temperature, which was calculated as the arithmetic mean of the onset temperature of a first peak observed on DSC curves for binary mixtures. The sixth degree polynomial equation was used to fit the liquidus line.

The parameters of the eutectic point (E), established by extrapolation of liquidus line to the intersection with solidus line, were as follows:

– composition: weight fraction of SIM 7.0%, weight fraction of PLU 93.0%;

– temperature: 48.8 °C

2.3. Powder X-ray diffraction

The powder X-ray diffraction patterns of SIM, PLU and selected solid dispersion received by fusion (FUS) and kneading (KN) methods are depicted in Fig. 3. Several distinct peaks can be observed at diffraction angles (2θ) of 9.32, 10.89, 17.22, 18.76, 22.56 and 23.71 for SIM and also 19.12 and 23.33 for PLU, which indicate their crystalline properties. The XRD peaks of SIM and PLU in analyzed solid dispersion were observed at the same angular positions which confirm that no other, crystallographically different phase, was formed either during the kneading or the fusion process. However, the intensity of the peaks of SIM in both samples was significantly less than that of the pure drug, which could be attributed to the lower weight ratios of SIM incorporated in samples preparation compared

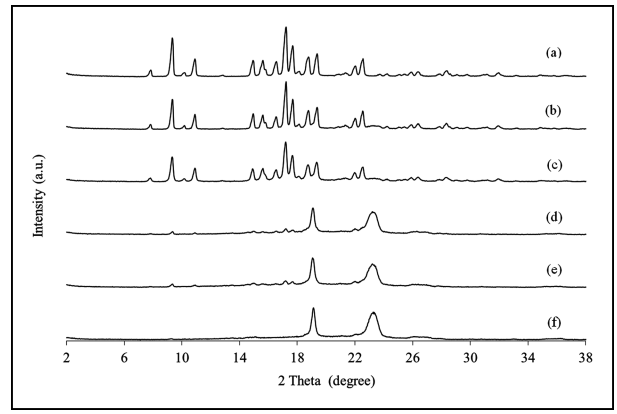

Fig. 3: XRPD patterns of: SIM (a), 90.0/10.0% w/w SIM/PLU-KN (b), 90.0/10.0% w/w SIM/PLU-FUS (c), 10.0/90.0% w/w SIM/PLU-KN (d), 10.0/90.0% w/w SIM/PLU-FUS (e), PLU (f).

to the carrier. Based on these results, the enhancement of SIM dissolution from 10.0/90.0 SIM/PLU were not related to the crystalline changes and could be due to the other factors, mainly particle size reduction and the solubilisation effect of the carrier. For the obtained mixtures of SIM and PLU no new diffraction peaks were registered, indicating the absence of a chemical interaction in the solid state between the two components.

2.4. Fourier transform infrared spectroscopy

FTIR spectroscopy was performed in order to identify any possible interaction between the drug and the carrier in solid state. Figure 4 demonstrates examples of the FTIR spectra of the pure drug, the polymer, and the solid dispersions obtained by two methods. The spectrum of pure SIM presented characteristic signals at 1267 cm^{-1} (C-O stretching vibration), 1469 cm^{-1} (CH_3 bending vibration), 1714 cm^{-1} (carbonyl stretching vibration), 2959 cm^{-1} and 3011 cm^{-1} (C-H stretching vibrations) and 3553 cm^{-1} (O-H stretching vibration). In addition, the main peaks of PLU appeared at 1111, 1280, 1344 and 2887 cm^{-1} which were related to the C-O stretching, CH_2 bending, O-H in-plane bending and C-H stretching aliphatic vibrations, respectively. The positions of the corresponding bands were similar in the spectra of solid dispersions and pure drug and polymer, suggesting that PLU did not interact with SIM when both, kneading and fusion methods, were used to prepare the solid dispersions.

2.5. Intrinsic dissolution study

The dissolution profiles of pure simvastatin and solid dispersions in 0.5% SLS at 37 ± 0.5 °C are shown in Fig. 5. It is evident that the dissolution rate of SIM improved in solid dispersion. Apparent IDR of various solid dispersions were measured and compared to that of pure SIM. Kaplan (1972) noted that compounds with IDR below 0.1 $mg/cm^2/min$ usually exhibited dissolution rate-limited absorption (Kaplan 1972). The IDR of pure SIM of 0.060 $mg/cm^2/min$ falls into this category. Table 2 shows the IDR of various formulations prepared by kneading and fusion methods. As expected, the increase in IDR was sensitive to the particular ratio of the drug to polymers utilized and the method of preparation. The intrinsic dissolution rate of SIM in solid dispersion prepared by the kneading method containing the substance by weight percentage of 50.0% w/w, 60.0% w/w and 69.9% w/w increased more than 20-fold. After 120 min of the test, more than 97% of SIM was released from the solid dispersion containing 60% w/w of SIM obtained by kneading

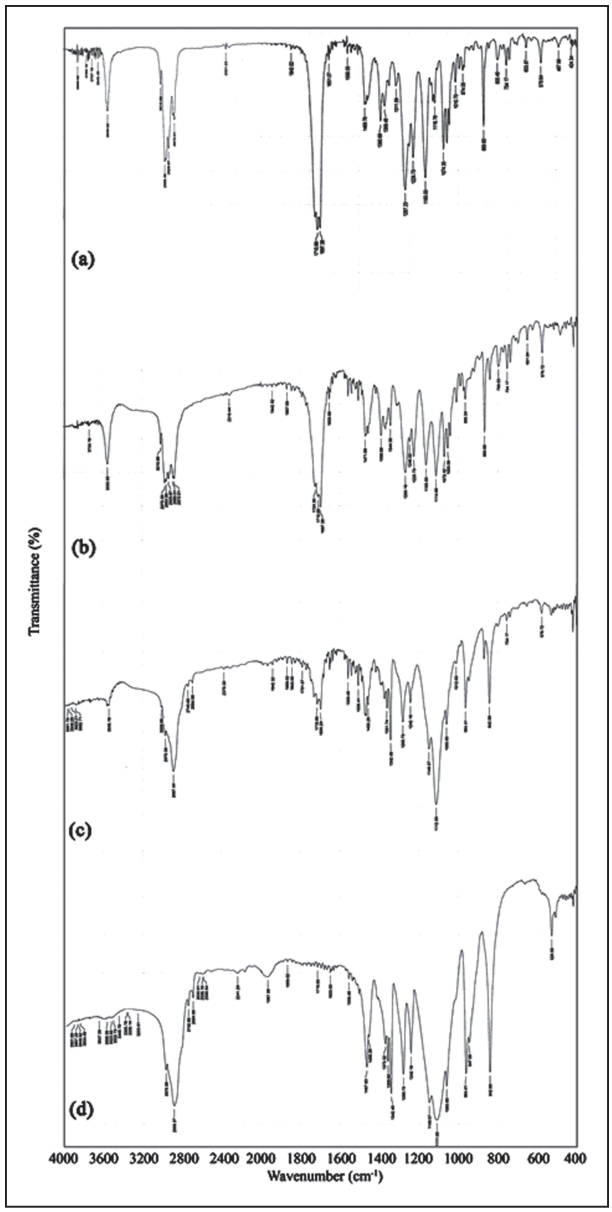

Fig. 4: Examples of FTIR spectra of: SIM (a), 80.0/20.0% w/w SIM/PLU-FUS (b), 20.0/80.0% w/w SIM/PLU-KN (c), PLU (d).

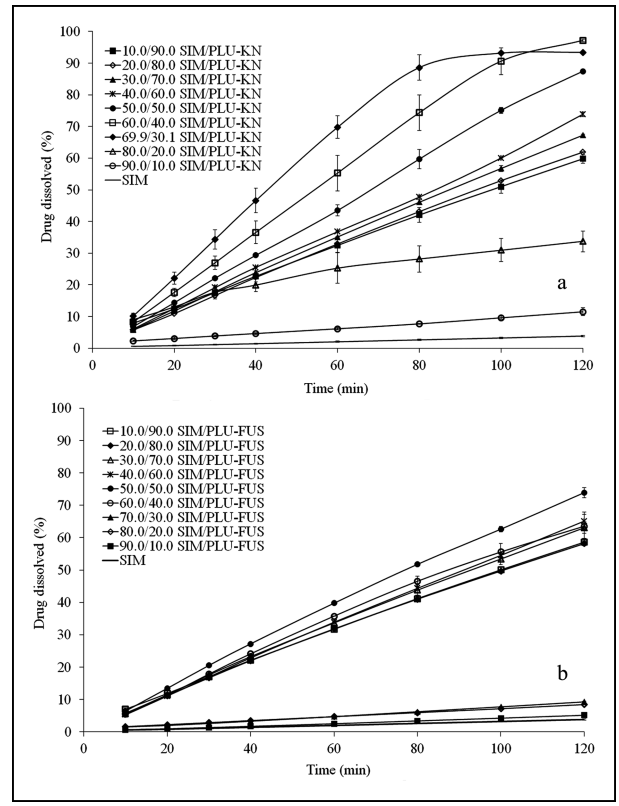

Fig. 5: Dissolution profiles of solid dispersions prepared by: a – kneading method, b – fusion method in 0.5% sodium sulfate aqueous solution. Data are expressed as mean ± SD (n = 3).

2.6. Summary and conclusions

Dissolution has an important role in the release of active ingredients from pharmaceutical preparations. Various polymers have been employed successfully to improve the dissolution of simvastatin in order to increase its bioavailability (Murtaza 2012), but there is no literature report on simvastatin solid dispersions with Pluronic F127. Our DSC studies demonstrate that the method, when at this time only 3.84% of pure SIM had been dissolved. The enhancement of dissolution of simvastatin from SDs might be due to the higher concentration of the polymer in SD that might have resulted in an increased wettability and dispersibility of the drug. Thus, the higher surfactant property of polymer could be responsible for the increased dissolution rate of SIM from SDs obtained by kneading and fusion methods in weight ratio from 10.0 to 60.0% w/w of substance. The lower increase of dissolution is observed for solid dispersions containing 70.0, 80.0 and 90.0% w/w of SIM obtained by fusing method.

SIM is classified as BCS Class II drug whose luminal dissolution rate is most likely the rate limiting step in the intestinal absorption, since all solid dispersions of SIM except for 90.0/10.0 SIM/PLU-FUS showed IDR greater than 0.1 mg/cm^2/min and are thus expected to show better bioavailability than pure SIM. The mechanism of increased dissolution rates of a drug from dispersions could be related to effective wetting of the reduced drug particles through an increase in surface area and solubilisation effect of the carrier (Craig 2002).

Table 2: Intrinsic dissolution rate (IDR) of pure simvastatin and prepared solid dispersions, and corresponding ratios

Formulation code	IDR (mg/cm^2/min)	R^2	IDR ratio SDs/SIM
10.0/90.0 SIM/PLU-KN	0.952 ± 0.0074	0.9994	16.00
20.0/80.0 SIM/PLU-KN	1.030 ± 0.0015	0.9988	17.31
30.0/70.0 SIM/PLU-KN	1.117 ± 0.019	0.9994	18.77
40.0/60.0 SIM/PLU-KN	1.206 ± 0.010	0.9990	20.26
50.0/50.0 SIM/PLU-KN	1.485 ± 0.012	0.9993	24.95
60.0/40.0 SIM/PLU-KN	1.699 ± 0.050	0.9943	28.55
69.9/30.1 SIM/PLU-KN	1.622 ± 0.034	0.9229	27.26
80.0/20.0 SIM/PLU-KN	0.433 ± 0.068	0.9521	7.27
90.0/10.0 SIM/PLU-KN	0.165 ± 0.024	0.9975	2.77
10.0/90.0 SIM/PLU-FUS	0.943 ± 0.021	0.9992	15.85
20.0/80.0 SIM/PLU-FUS	0.952 ± 0.0043	0.9979	16.00
30.0/70.0 SIM/PLU-FUS	1.040 ± 0.034	0.9985	17.48
40.0/60.0 SIM/PLU-FUS	1.085 ± 0.040	0.9994	18.23
50.0/50.0 SIM/PLU-FUS	1.223 ± 0.029	0.9981	20.55
60.0/40.0 SIM/PLU-FUS	1.073 ± 0.080	0.9942	18.03
70.0/30.0 SIM/PLU-FUS	0.143 ± 0.00060	0.9976	2.40
80.0/20.0 SIM/PLU-FUS	0.124 ± 0.00089	0.9999	2.08
90.0/10.0 SIM/PLU-FUS	0.082 ± 0.00030	0.9985	1.38
Pure SIM	0.060 ± 0.0024	0.9999	–

Data are expressed as mean ± SD (n = 3).

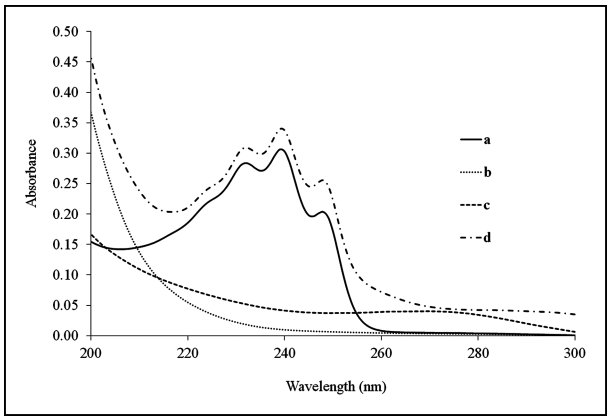

Fig. 6: UV spectra of aqueous solutions: SIM (a), PLU (b), 0.5% SLS (c) and solution containing SIM, PLU and SLS (d).

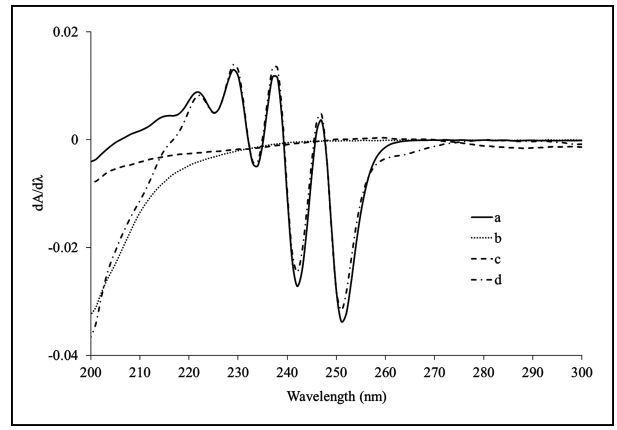

Fig. 7: 1D-UV spectra of aqueous solutions: SIM (a), PLU (b), 0.5% SLS (c) and solution containing SIM, PLU and SLS (d).

SIM/PLU solid dispersions formed a simple eutectic phase diagram. The FTIR spectroscopy and XRPD studies of the obtained mixtures showed no interaction between the components in solid state and confirmed the absence of terminal solid solutions. An examination of the dissolution rate of SIM from the obtained solid dispersions has confirmed an increase the dissolution rate of a drug in contact with a water solution. The results of this work suggest that the use of Pluronic F127 as a polymer carrier for simvastatin solid dispersions could be a promising approach to improve its release from oral dosage forms, and hence may affect its absorption rate.

3. Experimental

3.1. Materials

Simvastatin used in the study was a gift sample from Polpharma, Poland. Pluronic F127 was supplied from Fluka Biochemica, Germany. Sodium lauryl sulfate was purchased from P. P. H. "Stanlab", Poland. Potassium bromide was obtained from POCH, Poland. Ethanol HPLC grade was obtained from Fluka Biochemic, Germany. All other chemicals and reagents used in this study were of analytical grade.

3.2. Preparation of solid dispersions

Solid dispersions were prepared by mixing the appropriate amount of simvastatin and polymer by kneading and fusion methods. The total weight of each mixture was 5.0 g.

3.2.1. Kneading method (KN)

To the mixtures of drug and polymer in agate mortar sufficient volumes of ethanol were added to get a slurry-like consistency. The solvent was then completely evaporated at 40−45 °C with continuous stirring to obtain a dry mass. Nine solid dispersions of SIM/PLU were prepared. The weight ratios of the mixtures were 90.0/10.0, 80.0/20.0, 69.9/30.1, 60.0/40.0, 50.0/50.0, 40.0/60.0, 30.0/70.0, 20.0/80.0, and 10.0/90.0 per cent respectively. The obtained solid dispersions were stored under vacuum in a desiccator for 24 h. The dried solid residue was pulverized and passed through a 315 μm sieve. The resulting solid dispersions were stored in a desiccator at room temperature until used.

3.2.2. Fusion method (FUS)

Accurately weighed amounts of Pluronic F127 were mixed with different concentrations of simvastatin in a porcelain dish and heated on an electrical plate to 160 °C with continuous stirring to obtain homogeneous preparations, then rapidly cooled over an ice bath. The obtained solid dispersions were stored in a desiccator under a vacuum for 24 h, and then pulverized using an agate mortar and pestle. Nine solid dispersions of SIM/PLU were prepared. The weight ratios of the mixtures were 90.0/10.0, 80.0/20.0, 70.0/30.0, 60.0/30.0, 50.0/50.0, 40.0/60.0, 30.0/70.0, 20.0/80.0, and 10.0/90.0 percent respectively. The pulverized powders were sieved using a 315 μm sieve and then stored in a desiccator at room temperature until used.

3.3. Drug content

Solid dispersions equivalent to 20 mg of simvastatin were dissolved in 10 ml of ethanol. The received solutions were diluted in distilled water and determined at 238 nm by a UV-visible spectrophotometer (Jasco V-650, Japan) within the standard curve range between 1.0 and 3.0 mg/ml.

3.4. Differential scanning calorimetry (DSC)

The DSC curves of pure components and each mixture were obtained using a Mettler Toledo DSC 25 heat flow type differential scanning calorimeter. Measurements were driven by STAR^e software. Samples for DSC measurements were sealed in 40 μl standard aluminum crucibles with a single hole punched in the lid. The same type of empty crucible was applied as a reference. The DSC instrument was calibrated using the melting point of indium (156.6 ± 0.3) as a standard. DSC scans of each solid dispersion were performed at a heating rate of 5 °C/min in the temperature range of 25 to 160 °C. The DSC cell was purged with a stream of dry argon at a rate of 50 cm^3 min^{-1}.

3.5. Powder X-ray diffraction analysis (XRPD)

Powder X-ray diffraction patterns were recorded on a powder diffractometer D8 ADVANCE (Bruker, USA) with CuKα radiation with a Vantec position sensitive detector**.** The degree of diffractions was measured at 10°/min between 2° and 50° (2θ).

3.6. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were obtained using a IRAffinity-1 spectrophotometer (Shimadzu). Samples were mixed with potassium bromide (KBr) and compressed into a disc using the Specac hydraulic press (Mettler Toledo, Switzerland) before scanning from 4000 to 400 cm^{-1}.

3.7. Intrinsic dissolution study

The intrinsic dissolution studies were carried out for pure SIM and all of the prepared solid dispersions of SIM/PLU. The dissolution studies were done in water bath dissolution SR8-PLUS (Hanson, USA) fitted with a 7-channel peristaltic pump. The intrinsic dissolution rate was measured using the rotating disk method. SIM (100.0 mg) or an equivalent amount of solid dispersion discs were prepared by compressing powder in a Specac hydraulic press (Mettler Toledo, Switzerland) for 1 min under 1 t compression force, using a 8 mm punch. The die was mounted on the stirring drive mechanism and was rotated at 50 rpm. The dissolution test was conducted under sink conditions in 1000 mL of distilled water containing 0.5% SLS at 37 ± 0.5 °C. Samples were withdrawn at appropriate time intervals. Spectrophotometric analyses were performed on a JASCO-V-650 UV-Vis spectrophotometer with 1.00 cm quartz cells. Preliminary measurements of UV spectra of aqueous solutions of SIM, PLU and SLS have shown that these substances absorb in the wavelength range: 200 nm to 300 nm. The maximum absorbance wavelength for simvastatin solution was observed at 238 nm, and the UV spectrum of a solution of SLS showed a broad band in the range of 220 nm to 285 nm. Due to the overlap of the absorption bands (Fig. 6), it was impossible to direct the spectrophotometric determination of simvastatin in the studied formulations.

3.8. First derivative UV spectrophotometric method of simvastatin determination

Derivative UV spectra analysis (Fig. 7) showed that in the range of 245 nm to 270 nm the first derivative UV spectra (^{1}D-UV) did not overlap, so selective determinations of simvastatin could be done at a wavelength of 251 nm. The spectra were obtained with the instrumental parameters as follows: scan speed 200 nm min^{-1}; sampling interval 0.2 nm; spectral slit width 2 nm. The linearity of the method of first derivative was determined by preparing a series of standard solutions of simvastatin in 0.5% SLS in the concentration range 0.0005 – 0.0163 mg/mL. The spectra obtained for standard solutions were divided by the UV absorption spectrum of 0.5% solution of SLS, which was registered in relation to water as reference. Thus, the designated spectrum of comparison of spectra was subjected to differentiation. Quantification of simvastatin was based on the calibration curves representing a dependence of value of the first derivative (y) on concentration (x, mg/mL): $y = -185.7705\ x - 0.0475$ ($R^2 = 0.9976$). The limit of detection (LOD) for simvastatin was found to be 0.10 μg/ml and limit of quantitation (LOQ) was determinated as 0.35 μg/ml.

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